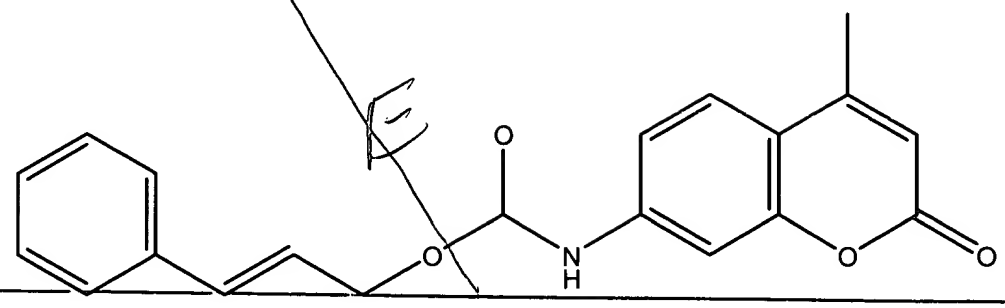

IN THE SPECIFICATION:

Please add the following abstract after page 48:

ABSTRACT

The present invention concerns prodrugs whose aromatic oxidation, particularly their enzymatic aromatic hydroxylation, results in their activation by the release of a drug moiety. It particularly concerns anti-tumor prodrugs and those which are specifically activated by the hydroxylation activity of the P-450 enzyme CYP1B1. Also provided are methods of detection of aromatic oxidation activity.

REMARKS

This amendment is in response to the Office Action dated December 5, 2002. Reconsideration of this application in view of the technical amendments and remarks made herein is respectfully requested.

Claims 37-52 are pending. Applicants have made technical amendments to claims 37, 42, 45, 48 and 52. New claim 57 has been added Support for amended claim 37 can be found in the art at the time the application was filed. Support for the amendment to claim 52 can be found in the specification at page 2, lines 3-7. Support for new claim 57 can be found in

original claim 48. No new matter has been added by the amendments to claims 37, 42, 45, 48 and 52 and by the addition of claim new 57.

In accordance with 37 C.F.R. §1.121, applicants have provided (1) accurate instructions to amend the claims, (2) replacement claims in clean form herein, and (3) another version of the amended claims marked up to show all the changes relative to the previous version of the claims, which appears on an attached page.

I. ELECTION/RESTRICTION

Applicants acknowledge that claims 53-56 have been withdrawn. The Examiner has rejected claims 37-41, and 49-52 as being drawn to an improper Markush group because the Markush group includes non-elected subject matter. The Examiner has suggested deleting reference to steroidal carbon framework and n>three. Accordingly, Applicants have amended claim 1 to delete reference to steroidal carbon framework and have amended n=0-6 to n=0-3. Applicants reserve the right to pursue this subject matter in divisional applications. Based on the amendments to the claims and the foregoing remarks, Applicants respectfully request that the rejection be withdrawn.

II. SPECIFICATION

The Examiner has indicated that the specification lacks an Abstract. Applicants have amended the specification to include the Abstract that was published in WO 99/40944, to which this application claims priority and have directed that the abstract be added as a separate page of the specification. Accordingly, Applicants have provided the abstract on a separate page herewith.

III. REJECTIONS UNDER 35 USC §112 ¶ 2:

Claims 37-42, 44 and 49-52 are rejected under 35 U.S.C. § 112, ¶ 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that the structural element in formula (Z) "Drug" of base claim 37 is indefinite alleging that Applicants have improperly attempted to define structure by function and further contends that defining a chemical structure solely by its principal biological property is improper.

Applicants respectfully disagree that the term "Drug" is indefinite and defines a structure by a biological property. The definition of the term "drug" in Webster's dictionary is "a substance used as medicine in the treatment of illness or disease." Webster's New College Dictionary, Houghton Mifflin Co. 1995, page 348 (attached hereto as Exhibit 1). The term "drug" defines a class of compounds which are used to treat a disease or illness. The term does not define a structure by a biological activity. The Examiner has acknowledged this himself in the Office Action by his description of the 102(b) prior art references (*e.g.* "where drug =5-flourourocil). In addition, the United States Patent and Trademark Office has consistently deemed similar claim language as patentable as illustrated by U.S. Patent No. 5,684,018 (claim 1), U.S. Patent No. 5,877,158 (claim 1), U.S. Patent No. 5,994,392 (claim 1), U.S. Patent No. 6,350,780 (claim 1) and U.S. Patent No. 6,395,266 (claim 16). Because a patent has a statutory presumption of validity, Applicants assert that these patents support that the use of the term "drug" in claims 37-42, 44 and 49-52 is proper.

The Examiner has also rejected claims 37-42, 44 and 49-52 under 35 U.S.C. § 112, second paragraph contending that the word "thiol" in the claims is indefinite alleging that

the term "thiol" is a carbon containing compound, not a univalent radical and that it is not clear if the bond from the thiol group is from the sulfur. Applicants respectfully disagree and point out that the term thiol is widely used in the art interchangeably with "mercapto" and "sulfhydryl". However to bring further clarity to the claims, Applicants have amended Claim 37 to recite the term "mercapto" rather than "thiol." Applicants assert that the knowledge in the art at the time the application was filed clearly supports this amendment. Exhibit 2 shows that these terms are used in the art interchangeably.

The Examiner further rejects claims 38-41, 44 and 49-52 under 35 U.S.C. § 112, second paragraph, alleging that the limitation in the claims "aromatic hydroxylation of the prodrug causes release of the drug moiety" is unduly functional. Again, the Examiner appears to be contending that the use of the term "drug" is defining a structure by a biological property. Applicants respectfully disagree for the same reasons set forth above. Furthermore, the aromatic hydroxylation of a drug is not a functional limitation but rather a limitation based on the change of the structure of the drug. Moreover, the specification clearly defines to the skilled artisan what is meant by aromatic hydroxylation of the drug.

Lastly, the Examiner rejects claim 42 under 35 U.S.C. § 112, second paragraph alleging that the limitation of "a phenanthyl group" in the last line of the claim is indefinite because there is no antecedent basis for this in claim 37 and because there is no way to form a tricyclic system from formula (Z) by joining R_2 and R_4. Applicants have amended claim 42 to delete reference that the framework includes a phenanthyl group.

For all of the foregoing reasons, Applicants respectfully request that the rejections of claims 47-42, 44 and 49-52 under 35 U.S.C. § 112, second paragraph, be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner has rejected claim 52 under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and use the invention. The Examiner alleges that Applicants lack enablement for the treatment of cancer generally. In response, Applicants have amended claim 52 to indicate that the tumor cell comprises an enzyme having aromatic hydroxylase activity. As indicated above, support for this amendment can be found throughout the specification and specifically at page 2, lines 3-7. Applicants assert that the specification fully enables the skilled artisan to practice claim 52 as amended. Therefore, Applicants request that the rejection of claim 52 under 35 U.S.C. § 112, first paragraph be withdrawn.

V. REJECTIONS UNDER 35 USC § 102(b)

Claims 37-42, 45 and 50-52 stand rejected under 35 USC § 102(b) as allegedly anticipated by Amble (Acta. Chem. Scand.), Pamer (Mol. Biochem. Parasitol.), Buur (Arch. Pharm. Chemi. Sci. Ed.), Grelan Pharmaceutical Co. (JP 56/016474 A2) or Suda (Biol. Pharm Bull).

Specifically, the Examiner alleges that Amble anticipates claims 37-42 and 45 because a compound taught by Amble fits formula (Z) with $X=R_1=R_2=R_3=R_4$=hydrogen, n=0, A is absent and drug = bis(2-chloroethyl)amine. Applicants have amended claim 37 such that X = OH, OMe, or $N(CH_3)_2$, and amended claim 45 to delete part (c).

The Examiner contends that Pamer anticipates claims 37-42 because a compound taught by Pamer fits formula (Z) with $X=R_1=R_2=R_3=R_4$=hydrogen, n=0, A = NH and drug = 4-methyl-2-oxo-2H-1-benzopyran. As noted above, Applicants have amended claims 37 such that X = OH, OMe, or $N(CH_3)_2$, and amended claim 45 to delete part (c)..

In addition, the Examiner contends that Buur anticipates claims 37-42 and 50-52 because Buur teaches a compounds that falls within formula (Z) with $X=R_1=R_2=R_3=R_4$=hydrogen, n=0, A is absent and drug = N1-(benzyloxycarbonyl-5-flourouracil). As noted above, Applicants have amended claim 37 such that X = OH, OMe, or $N(CH_3)_2$, and amended claim 45 to delete part (c).

Similarly, the Examiner alleges that Grenlan Pharmaceutical Co. anticipates claims 37-42 and 50-52 because a compound taught by Grenlan Pharmaceutical Co. falls within formula (Z) with $X=R_1=R_2=R_3=R_4$=hydrogen, n=0, A is absent and drug = 5-flourouracil. As noted above, Applicants have amended claim 37 such that X = OH, OMe, or $N(CH_3)_2$, and amended claim 45 to delete part (c).

Lastly, the Examiner alleges that Suda anticipates claims 37-42 and 50-52 because a compound taught by Suda falls within formula (Z) with $X=R_1=R_2=R_3=R_4$=hydrogen, n=0, A is absent and drug = 5-flourouracil. As noted above, Applicants have amended claim 37 such that X = OH, OMe, or $N(CH_3)_2$, and amended claim 45 to delete part (c).

Based on the revisions to claim 37, certain formulas in claim 48 became improperly dependent upon claim 37 because the X position of these formulas was an H. Therefore, to make sure claim 48 was in proper dependent format, Applicants have amended claim 48 to remove reference to formulas XXXI and XXXII. Applicants have added new claim 57 which is directed to formulas XXXI and XXXII.

Based on the amendments to claims 37 and 45, and the remarks made herein, Applicants assert that none of the cited prior art references anticipate the claims, as amended. Therefore, Applicants respectfully request that the rejection of claims 37-42, 45 and 50-52 under 35 U.S.C. § 102(b) be withdrawn.

VI. CONCLUSION

In view of the amendments to the claims and the remarks herein, Applicants maintain that Claims 37-52 and new claim 57 are now in condition for allowance. A Notice of Allowance is earnestly solicited.

Respectfully submitted,

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Patent Office Reg. No. 32,439

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Attorneys for Applicants

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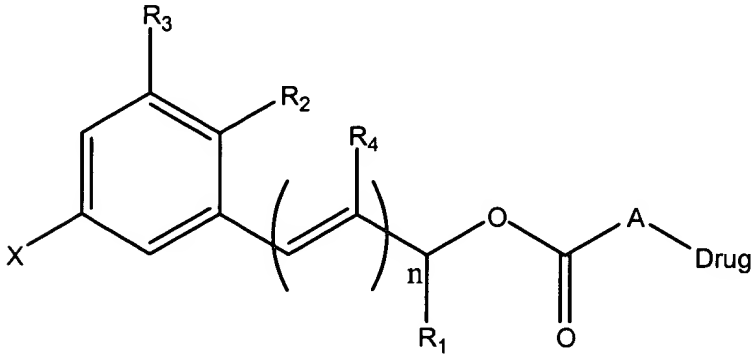
MARKED UP VERSION OF TECHNICAL AMENDMENTS

IN THE CLAIMS

Please rewrite the claims as follows:

37. (Amended) A prodrug comprising a drug moiety bound to a carrier framework having the formula (Z):



wherein:

X=[H,] OH, OMe or $N(CH_3)_2$; and
n=0-[6] 3;

and;

R_1=H, C_{1-4} lower alkyl, or together with R_2 forms part of a cycloalkyl group which may be further substituted to form part of a polycyclic cycloalkyl group[, or with R_2 forms part of a steroidal carbon framework];

R_2=H, OMe, C_{1-4} lower alkyl, or together with R_1 and/or R_3 forms part of a cycloalkyl, polycyclic cycloalkyl [or steroidal carbon framework], or forms part of a polycyclic aromatic group by linkage to R_4;

R_3=H, OMe, C_{1-4} lower alkyl or together with R_2 forms part of a cycloalkyl, polycyclic cycloalkyl[or steroidal carbon framework]; and

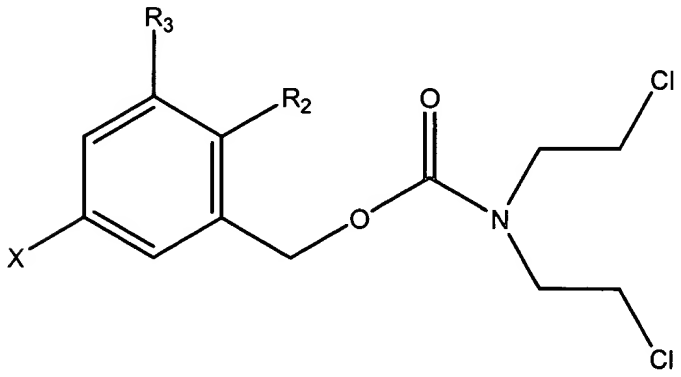
R_4=H or is fused directly to the aromatic position designated by R_2 and either:

the drug moiety is derived from a drug having a free amino, hydroxyl or [thiol] mercapto group and which links it to the rest of the prodrug, such that A represents NH, NR (R=C_{1-4} lower alkyl), O or S; or

the drug moiety is derived from a drug having a carboxylate group, an ester linkage joining it to the rest of the prodrug and A being absent.

42. (Amended) A prodrug according to claim 37 wherein the framework includes a[t least one selected from the group consisting of a]naphthyl group [and a phenanthyl group].

45. (Amended) A prodrug according to claim 44, having the general formula (Y):



R_2, R_3 and X being selected from any one of the group of:

a) R_2 = H, R_3 = H, X = OMe in Formula XVIII;

b) R_2 = H, R_3 = OMe, X = OMe in Formula XIX;

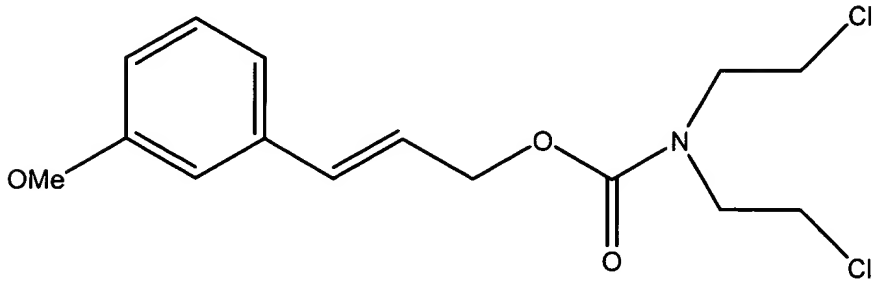
[c) R_2 = H, R_3 = H, X = H in Formula XX;

d) R_2 = OMe, R_3 = H, X = H in Formula XXI;] and

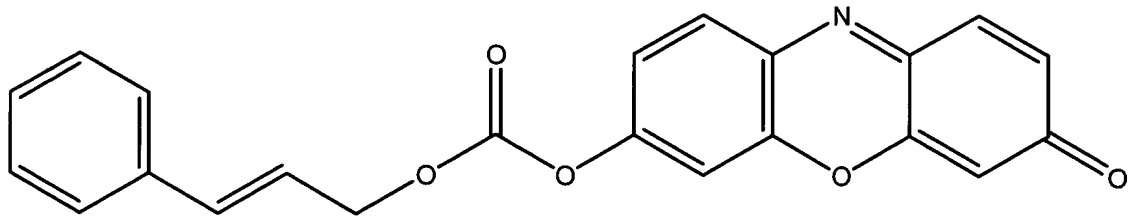
[e)] c) R_2 = OMe, R_3 = H, X = OMe in Formula XXII.

48. A prodrug according to claim 47, having a formula [selected from the group consisting] of:

(XXX):

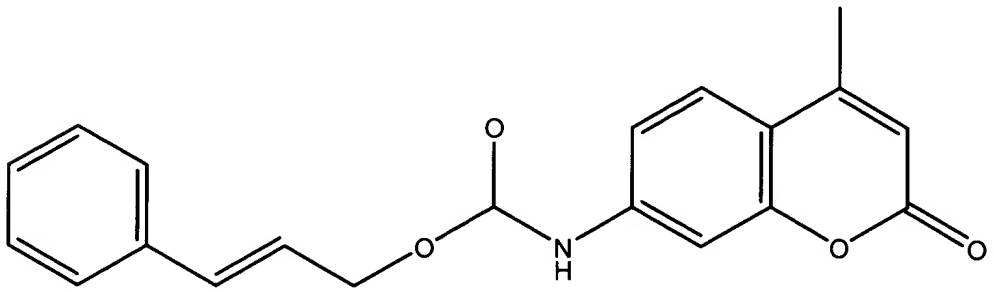


[(XXXI):



and

(XXXII):



].

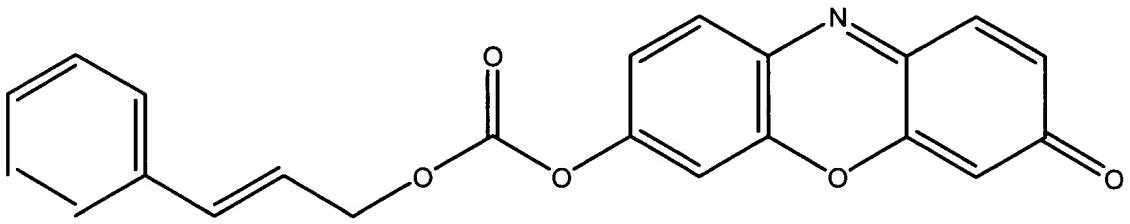
52. (Amended) A method of inhibiting tumor cell growth comprising:

contacting a tumor cell with a prodrug according to any one of claims 37 or 38, wherein the tumor cell comprises an enzyme having aromatic hydroxylase activity.

Please add the following new claim 57:

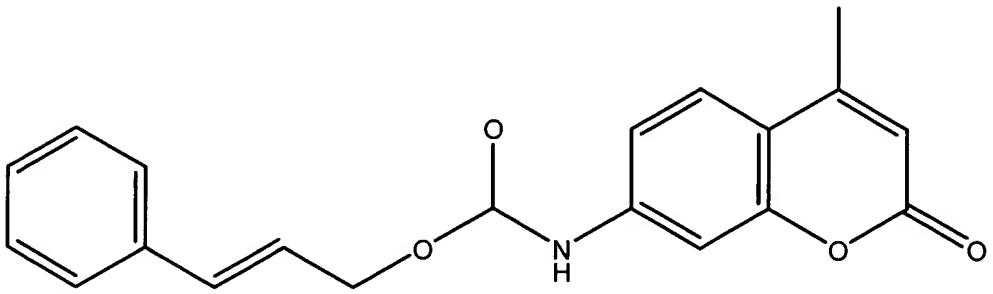
57. A prodrug comprising a drug moiety bound to a carrier framework having the formula selected from the group consisting of:

(XXXI):



and

(XXXII):



IN THE SPECIFICATION:

Please add the following abstract after page 48:

ABSTRACT

The present invention concerns prodrugs whose aromatic oxidation, particularly their enzymatic aromatic hydroxylation, results in their activation by the release of a drug moiety. It particularly concerns anti-tumor prodrugs and those which are specifically activated by the hydroxylation activity of the P-450 enzyme CYP1B1. Also provided are methods of detection of aromatic oxidation activity.